Journal of the American College of Cardiology
© 2006 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 48, No. 9 Suppl A
ISSN 0735-1097/06/$32.00
doi:10.1016/j.jacc.2006.07.006

Arrhythmia Predisposition

Between Rare Disease Paradigms and Common Ion Channel Gene Variants

Eric Schulze-Bahr, MD*†‡

Münster, Germany

Cardiac side effects, such as QT prolongation or occurrence of Torsade de pointes (TdP), from widely used cardiac and non-cardiac drugs are still a major challenge for physicians. Recent advances in knowledge on the physiology of myocardial repolarization have made it clear that alterations of ion channel genes are associated with diverse in vitro effects that may tune normal repolarization to critical edges where ventricular arrhythmia occurs. The extent to which genetic factors (aside from "typical" ion channel gene mutations) are associated with susceptibility to TdP remains to be determined and is addressed in this review. Future research must: 1) identify all relevant genes for repolarization; 2) determine the extent to which the variability of the QT interval and of the response to action potential prolongation is genetically controlled; 3) investigate the role of functionally relevant single nucleotide polymorphisms/haplotype constellations to the contribution to repolarization; and 4) integrate identified genetic factors with other known factors for TdP risk, according to their relative importance, in a network algorithm for arrhythmogenesis. Gaining an understanding of the current genetic and genomic data of patients with drug-induced arrhythmia are the first steps to overcoming the hurdles associated with unexpected cardiac side effects of a variety of drugs. (J Am Coll Cardiol 2006;48:67–78) © 2006 by the American College of Cardiology Foundation

Phenotypic variation in arrhythmia development is well known from families with inherited, arrhythmogenic disorders and also from patients with polygenic disorders, e.g. myocardial infarction, for which not every patient develops ventricular fibrillation during acute ischemia. Multiple factors, such as age, gender, and environmental conditions, play an important role in the modulation of the phenotype. The extent of genetically controlled variation is not clear to date, but it is of potential interest. Knowledge of contributing factors may be generally useful for addressing arrhythmia susceptibility independently of its cause and may become a (laboratory) tool for risk stratification. Recently, common protein variants in cardiac ion channels have been identified that may have a potential impact on arrhythmia susceptibility and pharmacogenetic strategies for arrhythmia circumvention and therapy. It is currently being investigated whether these gene variants help to explain the individual differences in arrhythmia development. The characterization of single gene disorders, which is still incomplete, has provided important insights into the molecular pathogenesis of cardiac arrhythmias. Emerging data on genotype/phenotype relations already exists and led to clinically relevant recommendations for gene-specific management of patients. Early genotyping now enables the identification of patients at high cardiac risk in a familial setting. In this review, the impact of common ion channel gene variants on acquired arrhythmogenic conditions is reviewed.

*From the Leibniz Institute for Arteriosclerosis Research (LIFA), Molecular Cardiology, University of Münster, Münster, Germany; the †Department of Cardiology and Angiology, University Hospital, University of Münster, Münster, Germany; and the ‡Interdisciplinary Center for Clinical Research (IZKF), Münster, Germany. This work was supported by the Leducq Foundation, Paris, France, and by the German Research Foundation, Bonn, Germany (DFG Schu1082/3-1 and 3-2, DFG Ki653/13-1, SFB 656-C1). Members of the FLQ project "Epidemiology of Inherited, Arrhythmogenic Disorders" were Isabelle Denjoy (Paris), Pascale Guicheney (Paris), Dirk Isbrandt (Hamburg), Olaf Pongs (Hamburg), Silvia Priori (Pavia), and Peter Schwartz (Pavia).

Manuscript received January 19, 2006; revised manuscript received April 28, 2006, accepted May 1, 2006.

INHERITED ARRHYTHMOGENIC DISORDERS AND ION CHANNEL GENES

"Primary electrical heart disease" refers to a group of rare, often familial, cardiac arrhythmias, in the absence of structural heart abnormalities. These disorders are mostly, but not exclusively (1–3), associated with mutations in cardiac ion channel genes. The long-QT syndrome (LQTS), short-QT syndrome (SQTS), Brugada syndrome (BrS), and catecholaminergic polymorphic ventricular tachycardia (CPVT) belong to this group. Together they account for 5% to 10% of sudden cardiac death (SCD) victims, and even more among the young (4–8). The population frequency of each arrhythmogenic disorder in the general population is not exactly known, but it is about 1 in 5,000 people for LQTS (9) and less for BrS (10–14). No information currently exists for CPVT and SQTS, but these disorders may have a significant contribution to idiopathic ventricular fibrillation (15,16). Recently, the term "electrical heart disease" came under discussion, as patients of these disorders were found to exhibit structural heart abnormalities (17–21,22). In the past, case reports already indicated, before the era of genetic testing, that structural changes may occur (23–27). Because not all SCD victims show structural abnormalities postmortem (e.g., sudden infant death syndrome cases), it may be true that some structural abnormal-

JACC Vol. 48, No. 9 Suppl A
November 7, 2006:67–78

Abbreviations and Acronyms

BrS = Brugada syndrome
CPVT = catecholaminergic polymorphic ventricular tachycardia
HERG = human ether-a-go-go gene
I = ionic current
LQTS = long-QT syndrome
SCD = sudden cardiac death
SNP = single nucleotide polymorphism
SQTS = short-QT syndrome
TdP = Torsade de pointes
VT = ventricular tachycardia

ities may occur as a consequence of aging (28). Therefore, these disorders are also classified as having "no apparent heart disease" (29) or as "ion channel cardiomyopathies" (30); exact nomenclatures will be addressed in future investigations.

Important insights into the pathogenesis of cardiac arrhythmias have been achieved from the molecular characterization of monogenic inherited arrhythmia syndromes (Table 1). The ion channel basis of congenital LQTS was discovered over 10 years ago by disease-causing mutations in the *KCNH2* gene (*HERG*) and *SCN5A* (Nav1.5), which are the genes encoding the cardiac delayed rectifier I_{Kr} potassium and I_{Na} sodium currents, respectively. Congenital LQTS is characterized by prolonged ventricular repolarization on the surface electrocardiogram (ECG) (i.e., QT prolongation) and ventricular tachyarrhythmias. Syncope and sudden death in LQTS patients may result from a distinctive polymorphic ventricular tachycardia (VT) called "Torsade de pointes" (TdP). Later, further heterogeneity of LQTS was shown by detecting mutations in the delayed rectifier I_{Ks} potassium channel gene *KCNQ1* (31,32) and the 2 genes for the small beta subunits KCNE1 and KCNE2 (33–37). Detailed reviews can be found elsewhere (38,39). A list of the more than 300 published LQTS mutations, which are more or less "private" (family-specific), and identified gene polymorphisms can be obtained on several web sites. In addition to these subforms, 3 related disorders with an extracardiac phenotype due to pleiotropic gene effects are known (Jervell and Lange-Nielsen syndrome, Andersen-Tawill syndrome, and Timothy syndrome) (32,36,40,41).

An unexpected phenotype complexity has been noted that gives patterns of "polygenic" (multifactorial) disease to inherited arrhythmia syndromes. This may be a result of multiple interactions of a gene mutation with individual or environmental factors or with modifier genes or gene variants. This interplay is thought to alter the expressivity of a specific phenotype from mild to pronounced even in carriers of the same mutation. As an example, cardiac sodium channelopathies (families with *SCN5A* mutations) show a broad, complex genotype-phenotype variety in the same family (i.e., members with an identical mutation), which leads to overlap syndromes or distinct clinical entities (42–45). Such studies highlight the hazards of predicting phenotype on the basis of gene mutations alone. Current efforts in risk stratification of these arrhythmia disorders (46–50) are on the way, but genetic and pathophysiological heterogeneity often make a clear correlation with clinical outcome difficult and less linear than anticipated.

ACQUIRED VENTRICULAR ARRHYTHMIAS AND IONIC CURRENTS

Acquired monomorphic and polymorphic VTs are more frequent and typically occur in the context of structural heart disease. Among all the possible factors, various triggers may determine arrhythmia susceptibility, but the role of genetic factors is probably small when there is no evidence for a monogenic cardiac disorder. Population-based studies still demonstrated an increased risk of SCD among patients with a parental history of cardiac arrest (8), but the genetic basis is not yet clear. Very recently, a quantitative influence on the myocellular repolarization due to (yet unidentified) genetic variation at several chromosomal loci has been described (51,52). Moreover, other risk factors (e.g., structural and electrical remodeling during acute ischemia, altered hemodynamic loads, or changes in neurohormonal signaling) are recognized key features that alter ion channel gene expression. Down-regulation of major repolarizing potassium currents, I_{to}, I_{Kr}, I_{Ks}, and I_{K1}, has been described in several models of heart failure and resembles a condition of "acquired QT prolongation." Cellular abnormalities through disturbances in the electrical cell-cell coupling and a local reduction of conduction velocity facilitate re-entrant ventricular arrhythmias. These cellular abnormalities can be found in the structurally diseased heart.

Drug-induced LQTS is another serious but reversible form of an acquired repolarization disturbance. The diagnosis depends upon demonstrating a significant prolongation of the QT interval during drug exposure and an exclusion of other causes of ventricular arrhythmia (e.g., serum potassium <2.5 mmol/l, acute coronary ischemia, structural heart disease). The QT interval prolongation extends to excessive values (more than +60 ms); it appears with T-wave lability/alternans and changes in T-wave morphology (negative or notched/biphasic), prominent (T)U waves, or marked increase in QT interval dispersion. This serious, adverse reaction to drug exposure is often accompanied by TdP and has led to several post-marketing withdrawals of drugs (e.g., terodiline in 1991, terfenadine in 1998, or levomethadyl recently). The incidence of drug-induced TdP is estimated to be at least 10 per million per year in Sweden (46). It is estimated that only a small fraction of these cases were recognized and reported. Other estimates based on prescription data suggest that exposure of 1% of the population to a torsadogenic drug doubles the risk ration for SCD and would account for about 10 deaths per million per year (53).

Table 1. Cardiac Ion Channel Disorders

Gene Symbols	Chromosomal Locus	Protein	Physiological Function	Inherited Disorder, Mode of Inheritance
KCNQ1	11p15.5	Potassium channel gene, α-subunit (K_vLQT1)	Myocellular repolarization (I_{Ks} current)	LQT1 (autosomal dominant or recessive ± inner ear deafness, sporadic, acquired) SQT2 (sporadic) AFib (autosomal dominant) SIDS (sporadic)
KCNH2 (HERG)	7q35-q36	Potassium channel gene, α-subunit	Myocellular repolarization (I_{Kr} current)	LQT2 (autosomal dominant or recessive, sporadic, acquired) SQT1 (autosomal dominant, +AFib) BrS2 (sporadic)
SCN5A	3p24-p21	Sodium channel gene, α-subunit (hH1)	Myocellular depolarization (I_{Na} current)	LQT3 (autosomal dominant or recessive, sporadic, acquired) BrS1 (autosomal dominant) (P)CCD (autosomal dominant) AVB (sporadic) AStST (autosomal dominant) SIDS (sporadic)
KCNE1	21q22	Potassium channel gene, β-subunit (minK)	Myocellular repolarization (I_{Ks} current)	LQT5 (autosomal dominant or recessive ± inner ear deafness)
KCNE2	21q22	Potassium channel gene, β-subunit (MirP)	Myocellular repolarization (I_{Kr} current)	LQT6 (autosomal dominant or sporadic)
KCNJ2	17q23	Potassium channel gene	Maintenance of resting potential, terminal repolarization (I_{Kir} current)	LQT7 (autosomal dominant or sporadic)
CACNA1c	12p13.3	Calcium channel gene	Myocellular depolarization ($I_{L,\ Ca++}$ current)	LQT8 (autosomal dominant or sporadic)
AnkB	4q25-q27	Anchoring protein linking integral membrane proteins to spectrin-actin cytoskeleton	Disruption or cellular organization; reduced protein levels of NCX, Na/K-ATPase, and $InsP_3R$; altered Ca^{2+} signaling	LQT4 (autosomal dominant, +AFib)
RyR2	1q42.1-q43	Cardiac ryanodine receptor	Ca^{2+} release channel of endoplasmic reticulum (electromechanical coupling)	CPVT (autosomal dominant, sporadic) IVF (sporadic)
CASQ2	1p13-p11	Calsequestrin	Ca^{2+} storage protein of endoplasmic reticulum (electromechanical coupling)	CPVT (autosomal recessive)
HCN4	15q24-q25	Cation channel gene	Spontaneous diastolic depolarization (I_f current)	SBr (sporadic, familial)

AFiB = atrial fibrillation; AStSt = atrial standstill; AVB = atrioventricular block; BrS = Brugada syndrome; CPVT = catecholaminergic polymorphic ventricular tachycardia; $InsP_3R$ = ionositol-1,4,5-phosphate-receptor; IVF = idiopathic ventricular fibrillation; LQTS = long-QT syndrome; (P)CCD = (progressive) cardiac conduction disease; SBr = sinus bradycardia; SIDS = sudden infant death syndrome; SQTS = short-QT syndrome.

Pathophysiologically, the hallmark mechanism of drug-induced LQTS is the blockade of the I_{Kr} channels (54–56), which are encoded by human ether-a-go-go gene (*HERG*), the LQT2/SQT1 gene (57,58). This affinity is due to 2 important structural characteristics: first, a larger inner cavity of I_{Kr} channels than that of any other voltage-gated K^+ channel, and second, a transmembranous (so-called S6−) domain that has 2 aromatic residues at the cytosolic site to bind larger, aromatic drugs. Some exceptions of non-I_{Kr} blocking drugs (e.g., arsenic trioxide or indapamide) with observed TdP exist. An I_{Kr} blockade prolongs the myocardial action potential, preferentially in the mid-layer cells and Purkinje fibers rather than in other tissue layers, because the former have lower I_{Ks} and higher I_{Na} and thus result experimentally in an increase of QT dispersion (59,60). The I_{Kr} blocking drugs usually demonstrate a reverse frequency-dependent effect. The degree of prolongation in action potential duration is more prominent

JACC Vol. 48, No. 9 Suppl A
November 7, 2006:67–78

Table 2. Types and Sequence Location of DNA Variation (70)

Polymorphism Type	Sequence Location	Predicted Protein and Potential Functional Effects	Occurrence in Genome	Potential Disease Impact
Nonsense	Coding	Prematurely truncated, most likely loss of protein function	Very low	High
Missense, non-synonymous	Coding, non-conserved	Altered amino acid chain, mostly similar protein properties	Low	Low (to high)
Missense, non-synonymous	Coding, conserved	Altered amino acid chain, mostly different protein properties	Low	Medium to high
Rearrangements (insertion/deletion)	Coding	Altered amino acid chain, mostly different protein properties	Low	High
Sense, synonymous	Coding	Unchanged amino acid chain, rarely an effect on exon splicing	Medium	Low (to medium)
Promoter and regulatory sequences	Non-coding, promoter/ UTR	Unchanged amino acid chain, but may affect gene expression	Low to medium	Low to high, depending on site
Intronic nucleotide exchange (<40 bp)	Non-coding, splice/ lariat sites	Altered amino acid chain, failed recognition of exonic structure	Low	Low to high, depending on site
Intronic nucleotide exchange (>40 bp)	Non-coding, between introns	Unchanged amino acid chain, rarely abnormal splicing or mRNA instability, site for gene rearrangements	Medium	Very low
Intergenic nucleotide exchange	Non-coding, between genes	Unchanged amino acid chain, may effect gene expression, site for gross rearrangements	High	Very low

bp = base pairs; UTR = untranslated region (5′ or 3′ region of a gene).

during a low heart rate, when the QT interval is longer. Moreover, concentration-dependent effects on the prolongation of the QTc interval are known for many drugs, with the exception of quinidine. Important co-factors for TdP development during drug I_{Kr} blockade are hypokalemia, hypomagnesemia, hypertrophy, and heart failure, all of which prolong the baseline action potential duration by reducing major repolarizing potassium currents. Gender is also another important modulating factor, for women have longer QT intervals and a greater propensity for drug-induced TdP (61–66), due to differences in the densities of I_{Kr} and I_{K1} currents but not of I_{Ks} and I_{to}. In contrast, men with BrS were reported to have a much more prominent I_{to} in the right ventricle (67).

COMMON ION CHANNEL GENE VARIANTS

The "rare disease paradigm" refers to the common hypothesis that genetic mutations for Mendelian disorders are rare in the general population and that these disorders have a low incidence because genetic mutations for Mendelian disorders are rare in the general population. Systematic sequencing of genes for rare arrhythmogenic disorders has shown to harbor a significant portion of "natural variance" (polymorphic sites, single nucleotide polymorphisms [SNPs]), which are assumed to alter the protein structure (non-synonymous changes). The idea that this "common genetic variance" may determine common phenotypes has expanded to more common arrhythmias. Research groups are currently trying to correlate SNP in ion channel genes with polygenic arrhythmogenic disorders (e.g., atrial fibrillation). All types of polymorphic sites were found in ion channel genes. They differ from their location within the genomic sequence (coding vs. non-coding areas), from the type of nucleotide exchange and the consequence for the amino acid sequence, and from the frequency (relative occurrence) in the human genome (Table 2). Polymorphisms with the potentially highest phenotypic disease impact are rare within the genome. For genetic association studies, more frequent polymorphisms (e.g., missense/non-synonymous or sense/synonymous) are used and require large case and control populations, because of the low phenotypic impact. Proposed guidelines have been developed that should facilitate the quality of association studies (68,69), including strategies to ascertain *heritability and exact phenotyping of a trait*, to perform *population stratification of cases and controls* (ethnicity, age, and gender distribution), *to select physiologically and genetically meaningful markers*, to address the *probability of association*, and to *replicate* initial results in independent studies. To date, only a few of the several thousand published association studies strictly meet criteria to ascertain a ("true") genetic association. For arrhythmogenic disorders, the majority of data are still unreplicated by independent investigators or studies. The potential of applying new approaches, such as the evaluation of genomic information or serial proteomic expression, is still difficult to achieve in practice. Differences in study outcome may be related to population stratification, study design, still inappropriate marker selection, and lack of statistical power (70). Discovery of meaningful SNP markers (e.g., indicating an elevated risk of SCD) is still far from being established.

The idea that common ion channel sequence variance may also contribute to a common arrhythmia and SCD susceptibility was driven by the identification of non-synonymous protein alterations and in vitro characterization showing subtle alterations differing from the wild-type (70–96). The details of ion channel gene SNPs are dis-

cussed in detail elsewhere (70). Results of ion channel alterations may be non-comparable or contradictory, because in-vitro experiments may not be standardized between different laboratories (73).

Ethnicity-specific and population-specific frequencies of the SNP allele in ion channel genes must be taken into account when performing association studies (71,72, 75,78,79,87,91,94,97–99). Researchers recently attempted to link the SNPs of cardiac ion channel genes with the QT interval length in a Caucasian population (51). Using a 2-step design (initial screen with many SNPs and a medium-size population, successive screen with a few SNPs with suggestive linkage in a confirmatory sample), the SNPs of 4 LQT genes (*KCNQ1*, *KCNH2*, *KCNE1*, and *KCNE2*) were investigated. A multivariate linear regression model (including heart rate, gender, and age as covariates) for QT interval calculation was developed (so-called QTc-RAS). The SNPs in the *KCNH2* (LQT2) and *KCNQ1* (LQT1) genes showed the strongest change on QTc-RAS (from +2.1 ms to −2.5 ms) when tested alone. When combining SNPs, quantitative additive effects were noted (e.g., for the *KCNH2*-K897T SNP (rs1805123). Previously, some (77,100), but not all, studies (87,95,101) suggested an effect on the QTc interval duration. Although these results at first suggest that myocardial repolarization is heritable as a quantitive phenotypic trait, they, in fact, already show the potential problems of association studies addressing the role of certain SNPs on a quantitative trait.

GENETIC ASPECTS OF DRUG-INDUCED QT PROLONGATION AND ECG PARAMETERS

Several studies have linked a prolonged, heart-rate adjusted, QT interval to an increased risk of cardiac death in patients with diseases other than LQTS and even in healthy individuals as well (102–106). The available studies on this are not consistent with each other (107,108). The occurrence of acquired LQTS and TdP is often not predictable in individual patients. Acquired forms share clinical features with the congenital variant of LQTS, and variants in genes for congenital LQTS have also been found in acquired LQTS (Table 3). Certainly, cardiac repolarization is modified by many genetic and non-genetic factors, and thus arrhythmia risk is polygenic, due to the combined influence of several components. Sotalol testing (2 mg/kg body weight intravenously) was able to unmask abnormal repolarization in patients with diagnosed acquired LQTS. After infusion, QTc increased moderately in controls (from 422 ± 17 ms to 450 ± 22 ms) but significantly in acquired LQTS subjects (from 434 ± 20 ms to 541 ± 37 ms) (109). Along these lines, 56% to 71% of patients who suffer from TdP were reported to have prolonged baseline QT intervals (110) and QT dispersion, compared with controls (e.g., when exposed to dofetilide or almokalant) (111). In the relatives of patients with acquired LQTS, intravenous quinidine significantly prolonged transmural dispersion of repolarization (T_{peak}-T_{end} interval), compared with the relatives of control subjects. Thus, it may indicate a heritable, but subtle, component in repolarization capacity (112). Whether these relatives are at risk for TdP development is not yet known. It is though known from congenital LQTS that the clinical profile of a subject is not useful for determining the clinical severity of other affected family members (113).

It is reasonable to assume that genetic factors modulate susceptibility for TdP development and that ECG parameters have features of a quantitative genetic trait. It has though been found that only 10% to 15% of patients with drug-induced LQTS carry variants in the coding regions of the known LQTS genes (86,95,114) that cover disease mutations in 70% to 80% of the congenital forms. This may still indicate an incompleteness of knowledge about the genes or genomic constellations that predispose a person to adverse drug reactions. A differentiation has been proposed between *indirect*, *direct*, and *compound* genetic effects, depending on their interaction with I_{Kr}-blocking drugs (115). Indirect effects of gene variants impair I_{Kr} channel function at baseline but do not increase drug sensitivity, whereas compound effects refer to alterations of both. *Direct* effects of LQTS variants are perhaps the most insidious variants, as they only increase sensitivity to drug blockade but cause no detectable or significant in vivo or in vitro phenotype before drug administration. In principle, the development of an abnormal QT prolongation and an increase of the torsadogenic potential may occur in a previously asymptomatic patient with congenital LQTS, in which the diagnosis was not yet known or known without precise knowledge of the drug's action-potential–prolonging properties. The list of drugs that prolong the QT interval and/or that were associated with TdP is increasingly long. A more complex situation may occur when an LQTS gene mutation causes only subtle or no repolarization changes. Currently, reports are available for genotype-phenotype data on the non-penetrance of LQTS gene mutations. They suggest a significant amount of incomplete penetrance (so-called silent mutation carriers with a normal QTc interval), ranging from 10% (LQT3) through 19% (LQT2) up to 36% (LQT1) (46).

Despite that the majority of drugs associated with QT prolongation bind particularly to I_{Kr} (*HERG*) channels, mutations in other than *HERG* have been described in patients with drug-induced LQTS (114,116–118). This was also reported for other proarrhythmic conditions such as hypokalemia (119). Instead, mutations of LQTS genes for these patients have also been found in I_{Na} or I_{Ks} channel genes (Table 3). These findings support the concept of the "repolarization reserve" (120), which refers to a variety of factors that concordantly and critically impair repolarization capacity toward the threshold for development of torsades. At least 2 or more (repolarization-disturbing) hits are involved ("multi-hit" hypothesis) (e.g., an LQTS gene mutation affecting repolarization [substrate] and drug-mediated I_{Kr} inhibition [enhancer/modifier]). Often, a par-

JACC Vol. 48, No. 9 Suppl A
November 7, 2006:67–78

Table 3. Ion Channel Gene Variants Identified in Patients With Drug-Induced QT Prolongation or TdP Occurrence

Gene	Current	Amino Acid Alteration	Drug/Setting	Functional Assay	Minor Allele	Reference
KCNE2	I_{Kr}	T8E	TMX/SMX; quinidine; amiodarone	E8-MIRP1 weakly reduced I_{Kr} current peak density; (CHO cells); SMX and TMX had almost no effect on wild-type channels, but SMX was reported to inhibit more than 50% of A8-MiRP1 at −40 mV; mutant channels were 4× more sensitive to SMX than wild-type	1.6%	(34,86,89)
	I_{Kr}	Q9E	Clarithromycin, low K^+		Rare in Caucasians, but not in African Americans	(34,71)
	I_{Kr}	M54T	Procainamide	T54-MiRP1 significantly reduced I_{Kr} current peak density (CHO cells); no influence on drug-related channel inhibition was seen	Rare	(89)
	I_{Kr}	M57T	Oxatomide	T57-MiRP1 significantly reduced I_{Kr} current peak density (CHO cells); no influence on drug-related channel inhibition was seen	Rare	(89)
	I_{Kr}	A116V	Quinidine	V116-MiRP1 significantly reduced I_{Kr} current peak density (CHO cells); no influence on drug-related channel inhibition was seen	Rare	(89)
KCNH2	I_{Kr}	M124T	Probucol	Co-expression of wild-type HERG and T124-HERG resulted in markedly smaller amplitudes of I_{Kr} (xenopus oocytes); probucol decreased the amplitude of the HERG tail current, decelerated the rate of channel activation, accelerated the rate of channel deactivation, and shifted the reversal potential to a more positive value	Rare	(137)
	I_{Kr}	R328C	Not reported		Rare	(138)
	I_{Kr}	P347S	Cisapride/clarithromycin		Rare	(86,139)
	I_{Kr}	R486H	Quinidine		Rare*	(114)
	I_{Kr}	A561P	Clobutinol	P561-HERG led to an intracellular trafficking defect; when co-expressed with wild-type HERG, voltage-dependence was shifted toward more negative potentials (3–3.5 mV); clobutinol further blocked heteromeric channels	Rare*	(140) (141)
	I_{Kr}	R784W	Amiodarone	W784-HERG mediated a reduced I_{Kr} current (by −75%) and a positive shift of voltage dependence of activation	Rare	(95)
KCNQ1	I_{Ks}	R243H	Halofantrine; hydrochinine		Rare*†	(114)
	I_{Ks}	Y315C	Cisapride	In-vitro expression of mutant KvLQT1 protein showed a severe loss of current with a dominant negative effect on the WT-KvLQT1 channel	Rare*	(116)
	I_{Ks}	R555C	Terfenadine		Rare	(117,142)
	I_{Ks}	R583C	Dofetilide	C583C-KvLQT1 mediated I_{Ks} was reduced by ~50% compared with wild-type, and the voltage dependence of activation was shifted positively by 19.6 mV (CHO cells)	Rare	(95)

Continued on next page

Table 3. Continued

Gene	Current	Amino Acid Alteration	Drug/Setting	Functional Assay	Minor Allele	Reference
SCN5A	I_{Na}	G615E	Quinidine	E615-SCN5A indistinguishable from wild-type mediated I_{Na} currents (tsa-201 cells)	Rare	(95)
	I_{Na}	L618F	Quinidine	E615-SCN5A indistinguishable from wild-type mediated I_{Na} currents (tsa-201 cells)	Rare	(95)
	I_{Na}	S1103Y	Amiodarone	Y1103-SCN5A mediated an increased I_{Na} channel activation (HEK 293)	7%–10% (African Americans or West Africans/ Caribbeans only)	(95)
	I_{Na}	F1250L	Sotalol	E615-SCN5A indistinguishable from wild-type mediated I_{Na} currents (tsa-201 cells)	Rare	(95)
	I_{Na}	P1825L	Cisapride	The C-terminal mutant P1825-SCN5A mediated I_{Na} current with slow decay and prominent TTX-insensitive, non-inactivating component (gain-of-function), a reduced peak density (loss of function), shifted voltage dependence of activation (more positive potentials) and of inactivation (more negative potentials) (tsA-201 cells);		(118)
				P1825-SCN5A channels showed impairment of intracellular trafficking (CHO cells) and failed to generate QT prolongation; exposure with cisapride rescued cell surface expression of P1825-SCN5A and exaggerating the LQT3 phenotype		(143)

*Heterozygous mutation carriers may have a normal QT interval; for SCNSA, amino acid residues are numerated according to positions on the long splice variant; †Reported from recessive forms of LQTS.

CHO = Chinese hamster ovarian; HERG = human ether-a-go-go gene; LQTS = long-QT syndrome; SMX = sulfamethoxazole; TdP = Torsade de pointes; TMX = trimethoprim; TTX = tetrototoxin.

ticular (gene-specific) co-factor (stressor/trigger) can be identified that finally leads to the occurrence of TdP (121). Other co-factors associated with a higher incidence of TdP are hypokalemia, a slower heart rate (e.g., recent conversion from atrial fibrillation), pre-existing cardiac disease (hypertrophy, myocardial infarction), and female gender or baseline QTc intervals above 460 ms. Genetic susceptibility to drug-induced LQTS has also been addressed for drug-metabolizing genes, notably *CYP2D6* and *CYP3A4*, as the degree of QTc prolongation usually correlates with the drug's serum level (exception: quinidine) and its metabolism. Thus, physicians need to be aware of some pharmacodynamic and pharmacokinetic interactions to understand the occurrence of potentially high concentrations. Genotypization of *CYP2D6* is currently available to individualize the dosage of metabolized drugs (122), and this is important, because of poor drug metabolization in 5% to 10% of Caucasians and African Americans. For *CYP3A4*, allelic variants are not consistently associated with drug metabolizing activity, and, therefore, genotyping has become less relevant. In addition to inborn genetic variation, both cytochromes may exhibit altered gene expression and activity in the context of other conditions (e.g., in the elderly, with common food or co-administered drugs [e.g., erythromycin and other macrolide antibiotics, ketoconazole and other azole antifungals, and mibefradil]) (123). Thus, pharmacodynamic interactions (e.g., several QT prolonging drugs) and pharmacokinetic interaction (e.g., with drug clearance of a QT prolonging drug) should be carefully considered.

In acquired LQTS syndrome, efforts were focused on the frequency of LQTS polymorphisms, because mutations are not predominant. Yang et al. (95) screened the coding regions of the 3 major LQT genes (LQT1-3) in 92 patients with drug-induced LQTS and additional controls. The allele frequencies of 3 common, non-synonymous polymorphisms (*SCN5A*-H558R, *SCN5A*-R34C, *HERG*-K897T) did not significantly differ between the 2 groups. Similar findings were reported by Paulussen et al. (86) and indicate no particular concomitant effect of the presence of an LQTS gene polymorphism and the occurrence of TdP. The role of KCNE2 (I_{Kr} beta subunit) variants in congenital and drug-induced LQTS (34,89,95) is still under discussion, as LQT6 (KCNE2) mutations are rare in congenital LQTS (35,124,125) and may exhibit only subtle or no in vitro effects on I_{Kr} currents (35,126). *SCN5A*-S1103Y (also

SCN5A-S1102Y, referring to the shorter splice form of *SCN5A*) is another frequent LQT gene polymorphism that is possibly related to drug-induced LQTS. It has been identified primarily in West Africans and Carribeans (around 19%) and in African Americans (around 13%) (91). In contrast, it was not found in a sample of 511 Caucasians and 578 Asians, and it was rare in Hispanics (1 in 123) (91). *SCN5A*-Y1103 SNP was first identified in a 36-year-old female African American with idiopathic dilated cardiomyopathy, hypokalemia, and abnormal QT prolongation and TdP during amiodarone treatment. In the subject's family, the *SCN5A*-Y1103 allele was associated with a longer QT interval (YY carriers: QTc 464 ± 22 ms, n = 7; SY carriers: QTc 458 ± 22 ms, n = 10; SS carriers: 415 ± 24 ms, n = 10; p = 0.0014, analysis of variance [ANOVA]), although most of the YY or SY carriers were asymptomatic and had a normal repolarization. The presence of another LQTS gene mutation was not excluded. When 23 unrelated "arrhythmia cases" were investigated, a quantitative effect of the Y1103 allele on the QTc interval was not seen (QTc: in YY carriers 495 ± 35 ms, n = 2); in SY carriers 460 ± 29 ms, n = 11; in SS carriers 453 ± 44 ms (n = 9 + 1); p = 0.3570; ANOVA. Despite the fact that Y1103 allele carriers (YY or SY) had a higher relative risk for ventricular arrhythmia occurrence (91), this observation was obviously unlinked to baseline repolarization parameters. In-vitro studies demonstrated only subtle changes in I_{Na} channel activation (increased activation, greater peak amplitude, and larger sustained current) without a discernible effect on simulated action potentials until an (drug-induced) I_{Kr} block was present (91).

Is the degree of heritability known for ECG parameters? Very little data exist on this. Twin studies have been used to examine the effect of genetic variance on ECG parameters (129). PR interval, QRS duration, QRS axis, QTc, and ventricular rate were significantly determined by genetic effects, ranging from 30% to 60%. In another twin study, Busjahn et al. (127) showed in 100 healthy monozygotic and 66 healthy dizygotic twins that a significant portion (52%) of the variation of the QT interval was attributable to genetic factors. Heritability was also found for the duration of the P wave (46%) and for the QRS width (40%). Using microsatellite markers, QTc duration was quantitatively determined by the LQT1 and LQT4 loci, whereas QRS and T-wave axis appeared to be influenced by the LQT2 locus (127). In addition, population-based studies such as the National Heart, Lung, and Blood Institute Family Heart Study estimated the heritability of the QT interval duration. Here, Hong et al. (128) found evidence of a major genetic effect accounting for 11% of the variation in QT interval duration and multiple other effects accounting for another 34%. Similarly, Newton-Cheh et al. (52) found 35% heritability of QT interval duration. A genome-wide linkage analysis reported suggestive evidence for linkage of the QT interval to chromosome 3p (maximum multipoint LOD score of 2.84 at 24.4 cM). No linkages were found to known ion channel genes, including *SCN5A* (LQT3) on chromosome 3p, so the causal gene remains to be determined. All together there is broad evidence that QT interval duration is a heritable trait in a complex genetic setting.

CONCLUSIONS AND FUTURE DIRECTIONS

Recent advances in knowledge of the physiology of myocardial repolarization have made it clear that genetic alterations of key molecular components, such as ion channels, are associated with opposite in vitro effects of ionic current regulation, which may tune normal repolarization to critical edges where ventricular arrhythmia may occur (129). The extent to which genetic factors, aside from repolarization "typical" ion channel gene mutations, are associated with susceptibility to TdP remains to be determined. It also remains to be determined whether these are specific to particular classes of drugs with a proarrhythmic propensity. Following the concept of "repolarization reserve" (120), it is likely that TdP occurrence, upon an individual background of a genetic predisposition, would be independent of specific drugs and more linked to a drug's propensity to alter myocardial repolarization. As shown in Table 3, not only I_{Kr} channel gene mutations but also I_{Na} or I_{Ks} can be identified in patients with drug-induced TdP and I_{Kr} channel block. Animal models with chronic complete atrioventricular block and in-vitro studies have reported a high incidence of TdP as a result of a significant down-regulation of both I_{Ks} and I_{Kr} channels (130,131). Aiba et al. (132) showed that, in addition to drug-induced I_{Kr} channel block, subclinical I_{Ks} dysfunction, mimicking *KCNQ1* (LQT1) defects, could be a risk for drug-induced TdP, when other repolarizing currents such as I_{Kr} cannot maintain normal repolarization capacity. Vice versa, I_{Ks} may function as a repolarization reserve when the rapidly delayed rectifier I_{Kr} is reduced by disease or drug. Thus, I_{Ks} can prevent excessive action potential prolongation and development of early afterdepolarizations, which are precursors of TdP (133,134). Moreover, direct physical interactions between I_{Kr} and I_{Ks} channel subunits have been proposed (135,136); this would make considerations on the functional effects of LQT gene mutations or gene variants more complex than previously anticipated.

For the comprehensive assessment of genetic factors in drug-induced TdP, future research must:

- Identify all relevant genes for repolarization, as the portion of causative genes (e.g., for congenital LQTS), is still incomplete;
- Determine the extent to which the variability of the QT interval and of the response to action potential prolongation is genetically controlled;
- Investigate the role of functionally relevant SNPs and haplotype constellations in LQTS and other gene loci for their quantitative contribution to repolarization; and

- Integrate identified genetic factors with other known factors for TdP risk, according to their relative importance, in a network algorithm for arrhythmogenesis.

The genetic and genomic understanding of drug-induced arrhythmia is still in its infancy. For the majority of LQTS SNPs, valid, confirmatory data from independent genetic association studies are still lacking, and for some SNPs, conflicting genetic and in vitro data have been reported. There are still major hurdles to overcome (e.g., large, powerful studies need to be performed [in various ethnic groups]). Standardization of in vitro functional assessment of non-synonymous SNPs is needed to compare lab-specific results. These data should be available within the next few years and advances, along with additional technological improvements, will enable researchers to lower the costs of complex genotyping. A major effort will be required from scientists, physicians, and industry to overcome these hurdles and to realize the concept of "the right drug for the right patient."

Reprint requests and correspondence: Dr. Eric Schulze-Bahr, Molekular-Kardiologie, Leibniz-Institut für Arteriosklerose-forschung (LIFA) an der Westfälischen Wilhelms-Universität Münster, Domagkstr. 3, D-48149 Münster, Germany. E-mail: Eric.Schulze-Bahr@ukmuenster.de.

REFERENCES

1. Mohler PJ, Schott JJ, Gramolini AO, et al. Ankyrin-B mutation causes type 4 long-QT cardiac arrhythmia and sudden cardiac death. Nature 2003;421:634–9.
2. Priori SG, Napolitano C, Tiso N, et al. Mutations in the cardiac ryanodine receptor gene (hRyR2) underlie catecholaminergic polymorphic ventricular tachycardia. Circulation 2001;103:196–200.
3. Eldar M, Pras E, Lahat H. A missense mutation in the CASQ2 gene is associated with autosomal-recessive catecholamine-induced polymorphic ventricular tachycardia. Trends Cardiovasc Med 2003;13:148–51.
4. Myerburg RJ. Sudden cardiac death in persons with normal (or near normal) hearts. Am J Cardiol 1997;79:3–9.
5. Myerburg RJ, Interian A Jr., Mitrani RM, Kessler KM, Castellanos A. Frequency of sudden cardiac death and profiles of risk. Am J Cardiol 1997;80:10–9F.
6. Wever EFD, de Medina EOR. Sudden death in patients without structural heart disease. J Am Coll Cardiol 2004;43:1137–44.
7. Arking DE, Chugh SS, Chakravarti A, Spooner PM. Genomics in sudden cardiac death. Circ Res 2004;94:712–23.
8. Spooner PM, Albert C, Benjamin EJ, et al. Sudden cardiac death, genes, and arrhythmogenesis: consideration of new population and mechanistic approaches from a National Heart, Lung, and Blood Institute workshop, part I. Circulation 2001;103:2361–4.
9. Moss AJ, Kass RS. Long QT syndrome: from channels to cardiac arrhythmias. J Clin Invest 2005;115:2018–24.
10. Oe H, Takagi M, Tanaka A, et al. Prevalence and clinical course of the juveniles with Brugada-type ECG in Japanese population. Pacing Clin Electrophysiol 2005;28:549–54.
11. Blangy H, Sadoul N, Coutelour JM, et al. Prevalence of Brugada syndrome among 35,309 inhabitants of Lorraine screened at a preventive medicine centre [in French]. Arch Mal Coeur Vaiss 2005;98:175–80.
12. Greer RW, Glancy DL. Prevalence of the Brugada electrocardiographic pattern at the Medical Center of Louisiana in New Orleans. J La State Med Soc 2003;155:242–6.
13. Matsuo K, Akahoshi M, Nakashima E, et al. The prevalence, incidence and prognostic value of the Brugada-type electrocardiogram: a population-based study of four decades. J Am Coll Cardiol 2001;38:765–70.
14. Hermida JS, Lemoine JL, Aoun FB, Jarry G, Rey JL, Quiret JC. Prevalence of the Brugada syndrome in an apparently healthy population. Am J Cardiol 2000;86:91–4.
15. Viskin S, Belhassen B. Polymorphic ventricular tachyarrhythmias in the absence of organic heart disease: classification, differential diagnosis, and implications for therapy. Prog Cardiovasc Dis 1998;41:17–34.
16. Viskin S, Zeltser D, Ish-Shalom M, et al. Is idiopathic ventricular fibrillation a short QT syndrome? Comparison of QT intervals of patients with idiopathic ventricular fibrillation and healthy controls. Heart Rhythm 2004;1:587–91.
17. Bezzina CR, Rook MB, Groenewegen WA, et al. Compound heterozygosity for mutations (W156X and R225W) in SCN5A associated with severe cardiac conduction disturbances and degenerative changes in the conduction system. Circ Res 2003;92:159–68.
18. McNair WP, Ku L, Taylor MR, et al. SCN5A mutation associated with dilated cardiomyopathy, conduction disorder, and arrhythmia. Circulation 2004;110:2163–7.
19. Coronel R, Casini S, Koopmann TT, et al. Right ventricular fibrosis and conduction delay in a patient with clinical signs of Brugada syndrome: a combined electrophysiological, genetic, histopathologic, and computational study. Circulation 2005;112:2769–77.
20. Olson TM, Michels VV, Ballew JD, et al. Sodium channel mutations and susceptibility to heart failure and atrial fibrillation. JAMA 2005;293:447–54.
21. Frustaci A, Priori SG, Pieroni M, et al. Cardiac histological substrate in patients with clinical phenotype of Brugada syndrome. Circulation 2005;112:3680–7.
22. Tiso N, Salamon M, Bagattin A, Danieli GA, Argenton F, Bortolussi M. The binding of the RyR2 calcium channel to its gating protein FKBP12.6 is oppositely affected by ARVD2 and VTSIP mutations. Biochem Biophys Res Commun 2002;299:594–8.
23. Phillips J, Ichinose H. Clinical and pathologic studies in the hereditary syndrome of a long QT interval, syncopal spells and sudden death. Chest 1970;58:236–43.
24. James TN, Froggatt P, Atkinson WJ Jr., et al. De subitaneis mortibus. XXX. Observations on the pathophysiology of the long QT syndromes with special reference to the neuropathology of the heart. Circulation 1978;57:1221–31.
25. Okada R, Kawai S. Histopathology of the conduction system in sudden cardiac death. Jpn Circ J 1983;47:573–80.
26. Bos I, Johannisson R, Djonlagic H. Morphologic alterations in the long Q-T syndrome. Light and electron microscopic observations in the conduction system and in sympathetic trunks. Pathol Res Pract 1985;180:691–6.
27. Bharati S, Dreifus L, Bucheleres G, et al. The conduction system in patients with a prolonged QT interval. J Am Coll Cardiol 1985;6:1110–9.
28. Beaufort-Krol GC, van Den Berg MP, Wilde AA, et al. Developmental aspects of long QT syndrome type 3 and Brugada syndrome on the basis of a single SCN5A mutation in childhood. J Am Coll Cardiol 2005;46:331–7.
29. Nava A, Cannas S, Martini B. More evidence-based data are required for a consensus on the aetiology of the so-called Brugada syndrome. Eur Heart J 2003;24:2072–3.
30. Corrado D, Basso C, Thiene G. Is it time to include ion channel diseases among cardiomyopathies? J Electrocardiol 2005;38:81–7.
31. Wang Q, Curran ME, Splawski I, et al. Positional cloning of a novel potassium channel gene: KVLQT1 mutations cause cardiac arrhythmias. Nat Genet 1996;12:17–23.
32. Neyroud N, Tesson F, Denjoy I, et al. A novel mutation in the potassium channel gene KVLQT1 causes the Jervell and Lange-Nielsen cardioauditory syndrome. Nat Genet 1997;15:186–9.
33. Splawski I, Tristani-Firouzi M, Lehmann MH, Sanguinetti MC, Keating MT. Mutations in the hminK gene cause long QT syndrome and suppress IKs function. Nat Genet 1997;17:338–40.
34. Abbott GW, Sesti F, Splawski I, et al. MiRP1 forms IKr potassium channels with HERG and is associated with cardiac arrhythmia. Cell 1999;97:175–87.
35. Isbrandt D, Friederich P, Solth A, et al. Identification and functional characterization of a novel KCNE2 (MiRP1) mutation that alters HERG channel kinetics. J Mol Med 2002;80:524–32.

36. Schulze-Bahr E, Wang Q, Wedekind H, et al. KCNE1 mutations cause Jervell and Lange-Nielsen syndrome. Nat Genet 1997;17: 267–8.
37. Schulze-Bahr E, Schwarz M, Hoffmann S, et al. A novel long-QT 5 gene mutation in the C-terminus (V109I) is associated with a mild phenotype. J Mol Med 2001;79:504–9.
38. Kass RS, Moss AJ. Long QT syndrome: novel insights into the mechanisms of cardiac arrhythmias. J Clin Invest 2003;112:810–5.
39. Shah M, Akar FG, Tomaselli GF. Molecular basis of arrhythmias. Circulation 2005;112:2517–29.
40. Tristani-Firouzi M, Jensen JL, Donaldson MR, et al. Functional and clinical characterization of KCNJ2 mutations associated with LQT7 (Andersen syndrome). J Clin Invest 2002;110:381–8.
41. Splawski I, Timothy KW, Sharpe LM, et al. Ca(V)1.2 calcium channel dysfunction causes a multisystem disorder including arrhythmia and autism. Cell 2004;119:19–31.
42. Smits JP, Koopmann TT, Wilders R, et al. A mutation in the human cardiac sodium channel (E161K) contributes to sick sinus syndrome, conduction disease and Brugada syndrome in two families. J Mol Cell Cardiol 2005;38:969–81.
43. Veldkamp MW, Wilders R, Baartscheer A, Zegers JG, Bezzina CR, Wilde AAM. Contribution of sodium channel mutations to bradycardia and sinus node dysfunction in LQT3 families. Circ Res 2003;92:976–83.
44. Kyndt F, Probst V, Potet F, et al. Novel SCN5A mutation leading either to isolated cardiac conduction defect or Brugada syndrome in a large French family. Circulation 2001;104:3081–6.
45. Priori SG, Napolitano C, Schwartz PJ, Bloise R, Crotti L, Ronchetti E. The elusive link between LQT3 and Brugada syndrome: the role of flecainide challenge. Circulation 2000;102:945–7.
46. Priori SG, Schwartz PJ, Napolitano C, et al. Risk stratification in the long-QT syndrome. N Engl J Med 2003;348:1866–74.
47. Priori SG, Napolitano C, Gasparini M, et al. Natural history of Brugada syndrome: insights for risk stratification and management. Circulation 2002;105:1342–7.
48. Eckardt L, Probst V, Smits JP, et al. Long-term prognosis of individuals with right precordial ST-segment-elevation Brugada syndrome. Circulation 2005;111:257–63.
49. Brugada J, Brugada R, Brugada P. Determinants of sudden cardiac death in individuals with the electrocardiographic pattern of Brugada syndrome and no previous cardiac arrest. Circulation 2003;108: 3092–6.
50. Brugada J, Brugada R, Brugada P. Natural history in patients with the Brugada syndrome. Eur Heart J 2003;24:382.
51. Pfeufer A, Jalilzadeh S, Perz S, et al. Common variants in myocardial ion channel genes modify the QT interval in the general population: results from the KORA Study. Circ Res 2005;96:693–701.
52. Newton-Cheh C, Larson MG, Corey DC, et al. QT interval is a heritable quantitative trait with evidence of linkage to chromosome 3 in a genome-wide linkage analysis: the Framingham Heart Study. Heart Rhythm 2005;2:277–84.
53. Fitzgerald PT, Ackerman MJ. Drug-induced torsades de pointes: the evolving role of pharmacogenetics. Heart Rhythm 2005;2:S30–7.
54. Mitcheson J, Perry M, Stansfeld P, Sanguinetti MC, Witchel H, Hancox J. Structural determinants for high-affinity block of hERG potassium channels. Novartis Found Symp 2005;266:136–50.
55. Mitcheson JS, Chen J, Lin M, Culberson C, Sanguinetti MC. A structural basis for drug-induced long QT syndrome. Proc Natl Acad Sci U S A 2000;97:12329–33.
56. Sanguinetti MC, Jiang C, Curran ME, Keating MT. A mechanistic link between an inherited and an acquired cardiac arrhythmia: HERG encodes the IKr potassium channel. Cell 1995;81:299–307.
57. Curran ME, Splawski I, Timothy KW, Vincent GM, Green ED, Keating MT. A molecular basis for cardiac arrhythmia: HERG mutations cause long QT syndrome. Cell 1995;80:795–803.
58. Brugada R, Hong K, Dumaine R, et al. Sudden death associated with short-QT syndrome linked to mutations in HERG. Circulation 2004;109:30–5.
59. Antzelevitch C, Fish J. Electrical heterogeneity within the ventricular wall. Basic Res Cardiol 2001;96:517–27.
60. Antzelevitch C, Shimizu W. Cellular mechanisms underlying the long QT syndrome. Curr Opin Cardiol 2002;17:43–51.
61. Lehmann MH, Timothy KW, Frankovich D, et al. Age-gender influence on the rate-corrected QT interval and the QT-heart rate relation in families with genotypically characterized long QT syndrome. J Am Coll Cardiol 1997;29:93–9.
62. Lehmann MH, Hardy S, Archibald D, Quart B, Mac Neil DJ. Sex differences in risk of torsade de pointes with d,l sotalol. Circulation 1996;94:2535–41.
63. Locati EH, Zareba W, Moss AJ, et al. Age- and sex-related differences in clinical manifestations in patients with congenital long-QT syndrome: findings from the International LQTS Registry. Circulation 1998;97:2237–44.
64. Makkar RR, Fromm BS, Steinman RT, Meissner MD, Lehmann MH. Female gender as a risk factor for torsades de pointes associated with cardiovascular drugs. JAMA 1993;270:2590–7.
65. Wolbrette D, Naccarelli G, Curtis A, Lehmann M, Kadish A. Gender differences in arrhythmias. Clin Cardiol 2002;25:49–56.
66. Schulze-Bahr E, Kirchhof P, Eckardt L, Bertrand J, Breithardt G. Gender differences in cardiac arrhythmias [in German]. Herz 2005; 30:390–400.
67. Fish JM, Antzelevitch C. Cellular and ionic basis for the sex-related difference in the manifestation of the Brugada syndrome and progressive conduction disease phenotypes. J Electrocardiol 2003;36 Suppl:173–9.
68. Freely associating (editorial). Nat Genet 1999;22:1–2.
69. Cooper DN, Nussbaum RL, Krawczak M. Proposed guidelines for papers describing DNA polymorphism-disease associations. Hum Genet 2002;110:207–8.
70. Kääb S, Schulze-Bahr E. Susceptibility genes and modifiers for cardiac arrhythmias. Cardiovasc Res 2005;67:397–413.
71. Ackerman MJ, Tester DJ, Jones GS, Will ML, Burrow CR, Curran ME. Ethnic differences in cardiac potassium channel variants: implications for genetic susceptibility to sudden cardiac death and genetic testing for congenital long QT syndrome. Mayo Clinic Proceedings 2003;78:1479–87.
72. Ackerman MJ, Splawski I, Makielski JC, et al. Spectrum and prevalence of cardiac sodium channel variants among black, white, Asian, and Hispanic individuals: implications for arrhythmogenic susceptibility and Brugada/long QT syndrome genetic testing. Heart Rhythm 2004;1:600–7.
73. Anson BD, Ackerman MJ, Tester DJ, et al. Molecular and functional characterization of common polymorphisms in HERG (KCNH2) potassium channels. Am J Physiol Heart Circ Physiol 2004;286: H2434–41.
74. Aydin A, Bahring S, Dahm S, et al. Single nucleotide polymorphism map of five long-QT genes. J Mol Med 2005;83:159–65.
75. Chen JZ, Xie XD, Wang XX, Tao M, Shang YP, Guo XG. Single nucleotide polymorphisms of the SCN5A gene in Han Chinese and their relation with Brugada syndrome. Chin Med J (Engl) 2004;117: 652–6.
76. Friedlander Y, Vatta M, Sotoodehnia N, et al. Possible association of the human KCNE1 (minK) gene and QT interval in healthy subjects: evidence from association and linkage analyses in Israeli families. Ann Hum Genet 2005;69:645–56.
77. Gouas L, Nicaud V, Berthet M, et al. Association of KCNQ1, KCNE1, KCNH2 and SCN5A polymorphisms with QTc interval length in a healthy population. Eur J Hum Genet 2005;13:1213–22.
78. Iwasa H, Itoh T, Nagai R, Nakamura Y, Tanaka T. Twenty single nucleotide polymorphisms (SNPs) and their allelic frequencies in four genes that are responsible for familial long QT syndrome in the Japanese population. J Hum Genet 2000;45:182–3.
79. Iwasa H, Kurabayashi M, Nagai R, Nakamura Y, Tanaka T. Multiple single-nucleotide polymorphisms (SNPs) in the Japanese population in six candidate genes for long QT syndrome. J Hum Genet 2001;46:158–62.
80. Kubota T, Horie M, Takano M, et al. Evidence for a single nucleotide polymorphism in the KCNQ1 potassium channel that underlies susceptibility to life-threatening arrhythmias. J Cardiovasc Electrophysiol 2001;12:1223–9.
81. Lai LP, Deng CL, Moss AJ, Kass RS, Liang CS. Polymorphism of the gene encoding a human minimal potassium ion channel (minK). Gene 1994;151:339–40.
82. Lai LP, Su MJ, Yeh HM, et al. Association of the human minK gene 38G allele with atrial fibrillation: evidence of possible genetic control on the pathogenesis of atrial fibrillation. Am Heart J 2002;144:485–90.

83. Larsen LA, Andersen PS, Kanters J, et al. Screening for mutations and polymorphisms in the genes KCNH2 and KCNE2 encoding the cardiac HERG/MiRP1 ion channel: implications for acquired and congenital long Q-T syndrome. Clin Chem 2001;47:1390–5.
84. Maekawa K, Saito Y, Ozawa S, et al. Genetic polymorphisms and haplotypes of the human cardiac sodium channel alpha subunit gene (SCN5A) in Japanese and their association with arrhythmia. Ann Hum Genet 2005;69:413–28.
85. Makielski JC, Ye B, Valdivia CR, et al. A ubiquitous splice variant and a common polymorphism affect heterologous expression of recombinant human SCN5A heart sodium channels. Circ Res 2003;93:821–8.
86. Paulussen ADC, Gilissen RAHJ, Armstrong M, et al. Genetic variations of KCNQ1, KCNH2, SCN5A, KCNE1, and KCNE2 in drug-induced long QT syndrome patients. J Mol Med 2004;82: 182–8.
87. Pietila E, Fodstad H, Niskasaari E, et al. Association between HERG K897T polymorphism and QT interval in middle-aged Finnish women. J Am Coll Cardiol 2002;40:511–4.
88. Roden DM. Genetic polymorphisms, drugs, and proarrhythmia. J Interv Card Electrophysiol 2003;9:131–5.
89. Sesti F, Abbott GW, Wei J, et al. A common polymorphism associated with antibiotic-induced cardiac arrhythmia. Proc Natl Acad Sci U S A 2000;97:10613–8.
90. Simard C, Drolet B, Yang P, Kim RB, Roden DM. Polymorphism screening in the cardiac K+ channel gene KCNA5. Clin Pharmacol Ther 2005;77:138–44.
91. Splawski I, Timothy KW, Tateyama M, et al. Variant of SCN5A sodium channel implicated in risk of cardiac arrhythmia. Science 2002;297:1333–6.
92. Tan BH, Valdivia CR, Rok BA, et al. Common human SCN5A polymorphisms have altered electrophysiology when expressed in Q1077 splice variants. Heart Rhythm 2005;2:741–7.
93. Viswanathan PC, Benson DW, Balser JR. A common SCN5A polymorphism modulates the biophysical effects of an SCN5A mutation. J Clin Invest 2003;111:341–6.
94. Xie XD, Wang XX, Chen JZ, et al. Single nucleotide polymorphism in SCN5A and the distribution in Chinese Han ethnic group [in Chinese]. Sheng Li Xue Bao 2004;56:36–40.
95. Yang P, Kanki H, Drolet B, et al. Allelic variants in long-QT disease genes in patients with drug- associated torsades de pointes. Circulation 2002;105:1943–8.
96. Ye B, Valdivia CR, Ackerman MJ, Makielski JC. A common human SCN5A polymorphism modifies expression of an arrhythmia causing mutation. Physiol Genomics 2003;12:187–93.
97. Hwang HW, Chen JJ, Lin YJ, et al. R1193Q of SCN5A, a Brugada and long QT mutation, is a common polymorphism in Han Chinese. J Med Genet 2005;42:e7.
98. Iwasa H, Kurabayashi M, Nagai R, Nakamura Y, Tanaka T. Twenty single-nucleotide polymorphisms in four genes encoding cardiac ion channels. J Hum Genet 2002;47:208–12.
99. Wedekind H, Bajanowski T, Friederich P, et al. Sudden infant death syndrome and long QT syndrome: an epidemiological and genetic study. Int J Legal Med 2006. In press.
100. Bezzina CR, Verkerk AO, Busjahn A, et al. A common polymorphism in KCNH2 (HERG) hastens cardiac repolarization. Cardiovasc Res 2003;59:27–36.
101. Paavonen KJ, Chapman H, Laitinen PJ, et al. Functional characterization of the common amino acid 897 polymorphism of the cardiac potassium channel KCNH2 (HERG). Cardiovasc Res 2003;59:603–11.
102. Dekker JM, Schouten EG, Klootwijk P, Pool J, Kromhout D. Association between QT interval and coronary heart disease in middle-aged and elderly men. The Zutphen Study. Circulation 1994;90:779–85.
103. Siscovick DS, Raghunathan TE, Rautaharju P, Psaty BM, Cobb LA, Wagner EH. Clinically silent electrocardiographic abnormalities and risk of primary cardiac arrest among hypertensive patients. Circulation 1996;94:1329–33.
104. Whitsel EA, Raghunathan TE, Pearce RM, et al. RR interval variation, the QT interval index and risk of primary cardiac arrest among patients without clinically recognized heart disease. Eur Heart J 2001;22:165–73.
105. Whitsel EA, Boyko EJ, Rautaharju PM, et al. Electrocardiographic QT interval prolongation and risk of primary cardiac arrest in diabetic patients. Diabetes Care 2005;28:2045–7.
106. de Bruyne MC, Hoes AW, Kors JA, Hofman A, van Bemmel JH, Grobbee DE. Prolonged QT interval predicts cardiac and all-cause mortality in the elderly. The Rotterdam Study. Eur Heart J 1999;20: 278–84.
107. Goldberg RJ, Bengtson J, Chen ZY, Anderson KM, Locati E, Levy D. Duration of the QT interval and total and cardiovascular mortality in healthy persons (The Framingham Heart Study experience). Am J Cardiol 1991;67:55–8.
108. Ahnve S. QT interval prolongation in acute myocardial infarction. Eur Heart J 1985;6 Suppl D:85–95.
109. Kääb S, Hinterseer M, Nabauer M, Steinbeck G. Sotalol testing unmasks altered repolarization in patients with suspected acquired long-QT-syndrome—a case-control pilot study using i.v. sotalol. Eur Heart J 2003;24:649–57.
110. Zehender M, Hohnloser S, Just H. QT-interval prolonging drugs: mechanisms and clinical relevance of their arrhythmogenic hazards. Cardiovasc Drugs Ther 1991;5:515–30.
111. Houltz B, Darpo B, Edvardsson N, et al. Electrocardiographic and clinical predictors of torsades de pointes induced by almokalant infusion in patients with chronic atrial fibrillation or flutter: a prospective study. Pacing Clin Electrophysiol 1998;21:1044–57.
112. Kannankeril PJ, Roden DM, Norris KJ, Whalen SP, George AL Jr., Murray KT. Genetic susceptibility to acquired long QT syndrome: pharmacologic challenge in first-degree relatives. Heart Rhythm 2005;2:134–40.
113. Kimbrough J, Moss AJ, Zareba W, et al. Clinical implications for affected parents and siblings of probands with long-QT syndrome. Circulation 2001;104:557–62.
114. Schulze-Bahr E, Haverkamp W, Hördt M, Wedekind H, Borggrefe M, Funke H. Do mutations in cardiac ion channel genes predispose to drug-induced (acquired) long-QT syndrome (abstr)? Circulation 1997;96 Suppl:I–210.
115. Anantharam A, Markowitz SM, Abbott GW. Pharmacogenetic considerations in diseases of cardiac ion channels. J Pharmacol Exp Ther 2003;307:831–8.
116. Napolitano C, Schwartz PJ, Brown AM, et al. Evidence for a cardiac ion channel mutation underlying drug-induced QT prolongation and life-threatening arrhythmias. J Cardiovasc Electrophysiol 2000;11: 691–6.
117. Donger C, Denjoy I, Berthet M, et al. KVLQT1 C-terminal missense mutation causes a forme fruste long-QT syndrome. Circulation 1997;96:2778–81.
118. Makita N, Horie M, Nakamura T, et al. Drug-induced long-QT syndrome associated with a subclinical SCN5A mutation. Circulation 2002;106:1269–74.
119. Kubota T, Shimizu W, Kamakura S, Horie M. Hypokalemia-induced long QT syndrome with an underlying novel missense mutation in S4-S5 linker of KCNQ1. J Cardiovasc Electrophysiol 2000;11:1048–54.
120. Roden DM. Taking the "idio" out of "idiosyncratic": predicting torsades de pointes. Pacing Clin Electrophysiol 1998;21:1029–34.
121. Schwartz PJ, Priori SG, Spazzolini C, et al. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. Circulation 2001;103:89–95.
122. Kirchheiner J, Meineke I, Muller G, Roots I, Brockmoller J. Contributions of CYP2D6, CYP2C9 and CYP2C19 to the biotransformation of E- and Z-doxepin in healthy volunteers. Pharmacogenetics 2002;12:571–80.
123. Fujita K. Food-drug interactions via human cytochrome P450 3A (CYP3A). Drug Metabol Drug Interact 2004;20:195–217.
124. Splawski I, Shen J, Timothy KW, et al. Spectrum of mutations in long-QT syndrome genes. KVLQT1, HERG, SCN5A, KCNE1, and KCNE2. Circulation 2000;102:1178–85.
125. Tester DJ, Will ML, Haglund CM, Ackerman MJ. Compendium of cardiac channel mutations in 541 consecutive unrelated patients referred for long QT syndrome genetic testing. Heart Rhythm 2005;2:507–17.
126. Friederich P, Solth A, Schillemeit S, Isbrandt D. Local anaesthetic sensitivities of cloned HERG channels from human heart: comparison with HERG/MiRP1 and HERG/MiRP1(T8A). Br J Anaesth 2004;92:93–101.

JACC Vol. 48, No. 9 Suppl A
November 7, 2006:67–78

127. Busjahn A, Knoblauch H, Faulhaber HD, et al. QT interval is linked to 2 long-QT syndrome loci in normal subjects. Circulation 1999; 99:3161–4.
128. Hong Y, Rautaharju PM, Hopkins PN, et al. Familial aggregation of QT-interval variability in a general population: results from the NHLBI Family Heart Study. Clin Genet 2001;59:171–7.
129. Schulze-Bahr E. Short QT syndrome or Andersen syndrome: yin and yang of Kir2.1 channel dysfunction. Circ Res 2005;96:703–4.
130. Volders PG, Sipido KR, Vos MA, et al. Downregulation of delayed rectifier K(+) currents in dogs with chronic complete atrioventricular block and acquired torsades de pointes. Circulation 1999;100:2455–61.
131. Emori T, Antzelevitch C. Cellular basis for complex T waves and arrhythmic activity following combined I(Kr) and I(Ks) block. J Cardiovasc Electrophysiol 2001;12:1369–78.
132. Aiba T, Shimizu W, Inagaki M, et al. Cellular and ionic mechanism for drug-induced long QT syndrome and effectiveness of verapamil. J Am Coll Cardiol 2005;45:300–7.
133. Jost N, Virag L, Bitay M, et al. Restricting excessive cardiac action potential and QT prolongation. A vital role for IKs in human ventricular muscle. Circulation 2005;112:1392–9.
134. Silva J, Rudy Y. Subunit interaction determines IKs participation in cardiac repolarization and repolarization reserve. Circulation 2005; 112:1384–91.
135. Ehrlich JR, Pourrier M, Weerapura M, et al. KvLQT1 modulates the distribution and biophysical properties of HERG—a novel alpha-subunit interaction between delayed rectifier currents. J Biol Chem 2004;279:1233–41.
136. McDonald TV, Yu ZH, Ming Z, et al. A minK-HERG complex regulates the cardiac potassium current I(Kr). Nature 1997;388:289–92.
137. Hayashi K, Shimizu M, Ino H, et al. Probucol aggravates long QT syndrome associated with a novel missense mutation M124T in the N-terminus of HERG. Clin Sci (Lond) 2004;107:175–82.
138. Splawski I, Shen J, Timothy KW, Vincent GM, Lehmann MH, Keating MT. Genomic structure of three long QT syndrome genes: KVLQT1, HERG, and KCNE1. Genomics 1998;51:86–97.
139. Piquette RK. Torsade de pointes induced by cisapride/clarithromycin interaction. Ann Pharmacother 1999;33:22–6.
140. Bellocq C, Wilders R, Schott JJ, et al. A common antitussive drug, clobutinol, precipitates the long QT syndrome 2. Mol Pharmacol 2004;66:1093–102.
141. Chevalier P, Rodriguez C, Bontemps L, et al. Non-invasive testing of acquired long QT syndrome: evidence for multiple arrhythmogenic substrates. Cardiovasc Res 2001;50:386–98.
142. Berthet M, Denjoy I, Donger C, et al. C-terminal HERG mutations: the role of hypokalemia and a KCNQ1-associated mutation in cardiac event occurrence. Circulation 1999;99:1464–70.
143. Liu J, Laurita KR. The mechanism of pause-induced torsade de pointes in long QT syndrome. J Cardiovasc Electrophysiol 2005;16:981–7.